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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/802,644	03/09/2001	Jeff W. Lichtman	WSHU 2010.1	8528

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SENNIGER POWERS LEAVITT AND ROEDEL  
ONE METROPOLITAN SQUARE  
16TH FLOOR  
ST LOUIS, MO 63102

EXAMINER

WEBER, JON P

ART UNIT PAPER NUMBER

1651

DATE MAILED: 08/06/2002

12

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Applicati n N .

09/802,644

Applicant(s)

LICHTMAN ET AL.

Examiner

Jon P. Weber, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-40 is/are pending in the application.
- 4a) Of the above claim(s) 20-33 and 37-40 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-19 and 34-36 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4,5.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: .

***Status of the Claims***

Claims 1-40 have been presented for examination.

***Election/Restrictions***

Applicant's election with traverse of Group I, claims 1-19 and 34-36, and to the species of ion sensitive dye, and specific dye calcium indicates such as Oregon Green BAPTA 488 in Paper No. 7, filed 30 May 2002 is acknowledged. The traversal is on the ground(s) that the Groups are so related that there is no burden. This is not found persuasive because burden was established by the separate classification at least (MPEP 803) in the Office action of 30 April 2002.

The requirement is still deemed proper and is therefore made FINAL. Claims 20-33 and 37-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 5, 10 and 18 each recite "detecting the presence of said dye" as the last step. There is insufficient antecedent basis for this limitation in the claim. Each of the claims is drawn

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to a method of labeling, yet this last step contributes nothing to the labeling process. It is a post-processing step, which one does once the claimed process is complete. There are myriads of possible process steps that can be performed post-processing that do not further the claimed process.

Claims 34-37 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: steps where a cell label is actually generated. The method as claimed provides for placing nucleic acid into cells and nothing more.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The instant claims are directed to a method for staining cells where the staining dye is coated onto solid particles and the coated particles are propelled at the cell so as to stain the cell.

Claims 1-3 and 17, are rejected under 35 U.S.C. 102(b) as being anticipated by Haugland et al. (US 5,436,134) or Yue (US 5,656,449).

Both Haugland et al. (US 5,436,134) and Yue (US 5,656,449) disclose staining cells with neutral fluorescent cyanine dyes for nucleic acids. The stains have particular utility for staining reticulocytes (Abstract). When the nucleic acids are enclosed within cells, the dye can be transported into the cells “**by bombardment with solid particles coated with** or in the presence

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of **the dyes**" (Haugland - col. 7, lines 59-61; Yue - col. 9, lines 64-66). Any suitable means for detection of the stained cells may be used (Haugland - col. 8. line 58 to col. 9, line 10; Yue - column 12, lines 28-48). The method is suitable for use with live cells (Haugland - col. 2, lines 22-27; Yue - col. 2, lines 26-28). More than one dye having different fluorescent properties may be used as well as additional reagents to detect size, shape, physiology, etc. (Yue - col. 14, line 14 to col. 15, line 39).

Claims 1-2, 4, 10-11, 13 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Fitzpatrick-McElligott et al. (US 5,466,587).

Fitzpatrick-McElligott et al. (US 5,466,587) disclose a biolistic method of introducing substances into cells (sperm are preferred) wherein the biolistic particles upon which the substances are coated have a pure carbonaceous surface and a magnetic particle core. At col. 5, line 65 to col. 6, line 10, **biological stains** and **nucleic acids** encoding proteins to be expressed are included among the various substances that may be associated with these particles.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haugland et al. (US 5,436,134), Yue (US 5,656,449) and Fitzpatrick-McElligott et al. (US 5,466,587) in view

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of Magrassi et al. (1987), Gan et al. (1999) and Gee et al. (US 5,888,829) and further in view of Pichersky (US 5,849,526).

The teachings of Haugland et al. (US 5,436,134), Yue (US 5,656,449) and Fitzpatrick-McElligott et al. (US 5,466,587) have been discussed above. Haugland et al. (US 5,436,134), Yue (US 5,656,449) and Fitzpatrick-McElligott et al. (US 5,466,587) lack all of the dyes instantly claimed and do not use a stopping means to reduce aggregates.

Magrassi et al. (1987) disclose lipophilic dyes (Table 1) that were successfully used to stain living nerve terminals.

Gan et al. (1999) disclose lipophilic dyes such as DiO and DiI that are used to stain individual axons.

Gee et al. (US 5,888,829) disclose Oregon Green BAPTA as one of several well-known calcium sensitive dyes that can be used to detect calcium (column 9, lines 19-46).

Pichersky (US 5,849,526) discloses the use of blocking screens in microprojectile bombardment of cells (biolistics) with particles coated with DNA to transfect cells. The screen is believed to reduce the size of projectile aggregates (column 5, lines 38-54). Screens may be made, for example, from stainless steel or Nytex screen. The pore size of the screens is not set forth. N.B. Dellaporta (US 6,013,486) has the same teaching at column 6, line 53 to column 7, line 7, but is not relied upon as duplicative.

A person of ordinary skill in the art at the time the invention was made would have been motivated to use any suitable and available dye to stain cells in the method of Haugland et al. (US 5,436,134), Yue (US 5,656,449) and Fitzpatrick-McElligott et al. (US 5,466,587) because such dyes are well-known in the art for that purpose. Magrassi et al. (1987), Gan et al. (1999)

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and Gee et al. (US 5,888,829) are representative of the state of the art demonstrating that dyes with the desired properties that are sensitive to the substance to be detected and in the cell types of interest (neural) are known in the art.

A person of ordinary skill in the art at the time the invention was made would have been motivated to use a blocking means such as a screen to reduce the size of aggregates while allowing some coated particles to continue to the target cells in the method of Haugland et al. (US 5,436,134), Yue (US 5,656,449) and Fitzpatrick-McElligott et al. (US 5,466,587) because Pichersky (US 5,849,526) establish that uses such screen is an effective way to reduce damage to the cells from large aggregates.

The selection of a particular dye for staining purposes or the particular pore size of the screen is an arbitrary matter of experimental design choice of a result effective variable that is within the skill of the ordinary artisan to select.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use any suitable dye or a screen to block large aggregates in a biolistic method of labeling cells with dyes.

Claims 34-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (1998; ref 32) in view of Tsien (1998) and Matz et al. (1999).

Wong et al. (1998; ref 32) discloses staining retinal ganglion cells with GFP by transfection by biolistic means. Wong et al. (1998; ref 32) lack using multiple GFPs in the staining process.

Tsien (1998) discloses that there are many GFPs having different fluorescent properties.

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Matz et al. (1999) disclose that there are many fluorescent proteins analogous to GFP that can be used for the same purpose.

A person of ordinary skill in the art at the time the invention was made would have been motivated to combine multiple GFPs or other fluorescent proteins as taught by Tsien (1998) and Matz et al. (1999) in the method of Wong et al. (1998; ref 32) because different proteins are useful as multiple labels and reporters (page 539, Tsien), for example.

It is well-known in the art that multiple indicators provide multiple opportunities for selective identification. Providing multiple GFPs with different fluorescent properties allows multiple wavelength probes.

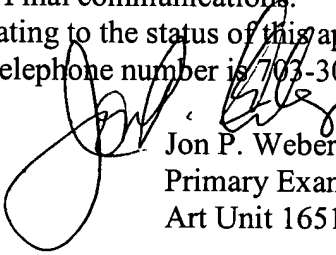
Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use multiple GFPs in the method of Wong et al. (1998; ref 32).

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P. Weber, Ph.D. whose telephone number is 703-308-4015. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Jon P. Weber, Ph.D.  
Primary Examiner  
Art Unit 1651

JPW  
August 2, 2002